REMARKS

Reconsideration of the rejection of all claims is respectfully requested in view of the above amendments and the following remarks.

Specification Amendments

Applicants note with appreciation the Examiner's careful review of the previous specification amendments, and the additional errors noted in subparagraphs a) through k) of the Action have rectified, with minor modification as noted below. The corrections made can easily be seen in the Appendix hereto, wherein added material is show by **bold underlined text** and deleted material is shown by **[bold text within brackets]**. The following modifications to the Examiner's suggested amendments are noted:

- With respect to subparagraph d) of the Action, the appropriate and consistent correction was to change "n is 0-4" to read --w is 0-4--. The "w" subscript in $-(CH_2)_w-$ is correct as is, but the superscript "CH^2" noted by the Examiner has been corrected.
- With respect to subparagraph h) of the Action, the change of "DCCI" to --DCI-- in the previous Amendment was an inadvertent error, and "DCI" has been changed back to --DCCI-- in the above amendments. Support for the term "DCCI" is found in the specification at page 43, line 2.
- A further inadvertent error introduced by the previous Amendment has also been corrected by further amendment to the first paragraph on page 32, line 4 to page 32, line 23, where the spelling of "dichloromethane" has been corrected.

Claim Amendments

Claim 7 has been amended to appropriately subscript the "t" in $(CH_2)_tOR^{6'}$ and $(CH_2)_tNR^{6'}R^{7'}$. Claim 8 has been amended to hyphenate "(2-methoxy-ethyl)" to be totally consistent with the naming of this compound in the specification at page 55, lines 5 and 6, as explained further below.

Following entry of these amendments, claims 7-9, 13 and 18-22 remain pending in this application.

Claim Rejections - 36 USC § 112

Claims 8, 9 and 18-22 have been rejection under section 112, first paragraph, as containing subject matter that is not described in the specification with respect to the amended compound of claim 8, which is asserted to lack support in the specification. This ground for rejection is respectfully traversed in that the compound of amended claim 8 is specifically disclosed and exemplified in specification Example 7. In order to avoid any possible question, the term "(2-methoxy-ethyl)" has been hyphenated in the above amendment to claim 8 so that the nomenclature used for the claimed compound is identical to the nomenclature used for the exemplified compound. It is therefore respectfully requested that this ground for rejection be withdrawn.

Claims 7, 9, 13 and 18-22 have been rejected under section 112, second paragraph, as being indefinite with respect to the "t" in the definition of the substituents on the aryl or heterocycle of $R^{2'}$, $R^{3'}$, $R^{3'}$ and $R^{5'}$. This ground for rejection is respectfully traversed. The term "t" is defined as being "1 to 4" immediately above the definition of $R^{2'}$, $R^{3'}$, $R^{3'}$ and $R^{5'}$ in claim 7. As noted above, claim 7 has been amended to appropriately subscript the "t" in

$(CH_2)_tOR^{6'}$ and $(CH_2)_tNR^{6'}R^{7'}$ to correct an inadvertent typographical error introduced with the previous Amendment. With the above explanation and correction of the typographical error, it is believed that any basis for this ground for rejection has been overcome, and withdrawal of this rejection is respectfully requested.

Conclusion

In view of the above amendments to the specification and claims and the foregoing remarks, it is believed that all remaining grounds for objection and/or rejection have been addressed and overcome. The specification and claims are now believed to be in proper form in all resects, and allowance of all claims is believed to be in order and is respectfully requested.

Respectfully Submitted,
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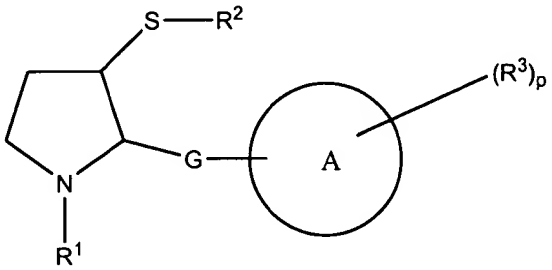
APPENDIX
VERSION WITH MARKINGS TO SHOW CHANGES

The following amendments have been made to the specification and claims, wherein added material is shown by **bold underlined text** and deleted material is shown by **[bold text within brackets]**:

IN THE SPECIFICATION

The specification at the first paragraph on page 2, line 6 to page 4, line 9, has been further amended as follows:

(Twice Amended) According to one aspect of the present invention there is provided an inhibitor of ras farnesylation of Formula I



wherein:

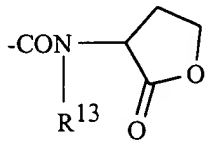
R^1 is selected from H; -C_{1-4}alkyl; -CO-C_{1-4}alkyl; -CO-O-C_{1-4}alkyl; -CO-O-C_{2-4}alkenyl; -C_{1-4}alkylene-CONR^{4}R^5 (wherein R^4 and R^5 are independently selected from H and C_{1-4}alkyl); -C_{1-4}alkylene-COOR^6 (wherein R^6 is selected from H and C_{1-4}alkyl); -C_{1-3}alkylene-Ph and -CO-O(CH $_2$)$_n$Ph wherein the phenyl groups in -C_{1-3}alkylene-Ph and -CO-O(CH$_2$)$_n$Ph are optionally substituted by R^a and/or R^b and R^a and R^b are independently selected from C_{1-4}alkyl, halogen, hydroxy, C_{1-4}alkoxy, C_{1-4}alkanoyl, C_{1-4}alkanoyloxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkanoylamino, nitro, cyano, carboxy, carbamoyl,

C_{1-4}alkoxycarbonyl, thiol, C_{1-4}alkylsulfanyl, C_{1-4}alkylsulfinyl,C_{1-4}alkylsulfonyl and sulfonamido; and n=0-4;

R^2 is selected from H; -C_{1-4}alkyl; -COC_{1-4}alkyl; and -$COOC_{1-4}$alkyl; and -C_{1-3}alkylene-Ph optionally substituted on the phenyl ring by R^a and or R^b;

R^3 is selected from H; OH; CN; CF_3; NO_2; -C_{1-4} alkyl; -C_{1-4}alkylene-R^7; -C_{2-4}alkenylene-R^7; -C_{2-4}alkynylene-R^7; R^7; OR^7 (where R^7 is selected from phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms selected from O, N and S and any aryl ring in R^7 is optionally substituted by R^a and/or R^b); C_{2-4}alkenyl; halogen; -$(CH_2)_yCOOR^8$ (where y = 0-3 and R^8 represents H, C_{1-4}alkyl, or C_{2-4}alkenyl); -$CONR^9R^{10}$ (where R^9 and R^{10} independently represent H, C_{1-4}alkyl, C_{2-4}alkenyl, -O-C_{1-4}alkyl, -O-C_{2-4}alkenyl or -C_{1-3}alkylenePh (wherein Ph is optionally substituted by R^a and R^b as hereinabove defined); -$CON(R^{11})OR^{12}$ (where R^{11} and R^{12} independently represent H, C_{1-4}alkyl or C_{2-4}alkenyl);

a group of Formula II: -$CONR^{13}$-$CR^{13a}R^{14}$-$COOR^{17}$, (where R^{13} and R^{13a} are independently H or C_{1-4}alkyl, R^{17} is H or C_{1-6}alkyl, R^{14} is selected from the side chain of a lipophilic amino acid, carbamoylC_{1-4}alkyl, N-(monoC_{1-4}alkyl)carbamoylC_{1-4}alkyl and N-(diC_{1-4}alkyl)carbamoylC_{1-4}alkyl, the group of Formula II having L or D configuration at the chiral alpha carbon in the corresponding free amino acid; a lactone of formula:



;

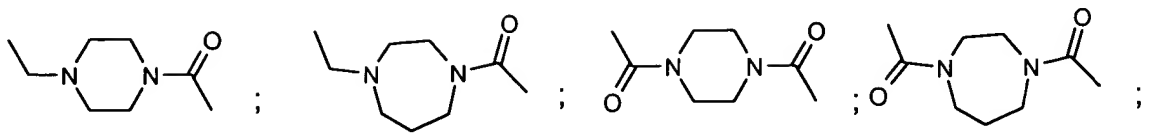
C_{1-4}alkyl monosubstituted on carbon with =N-OH;

a group of Formula -X-R^{15} (where X is selected from O, CO, CH_2, S, SO, SO_2 and R^{15} is selected from C_{1-6}alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms selected from O, N and S and any aryl ring in R^{15} is optionally substituted by R^a and/or R^b;

p is 0-3 in which R^3 values can be the same or different;

G is a linking moiety selected from the following groups written from left to right in

Formula I:



(wherein the piperazine and perhydro-1,4-diazepine rings are optionally substituted); $-CO-NR^{16}-$; $-CH_2-NR^{16}-$; $-CH_2S-$; $-CH_2O-$; $-CH_2-CHR^{16}$; $-CH=CR^{16}-$; $-CH_2NR^{16}-T-$; $-CH_2NR^{16}-SO_2-$; $-CH_2-NR^{16}-CO-T^1-$; $-CO-NR^{16}-T-$; $-CH_2S-T-$; $-CH_2O-T-$ (where R^{16} is selected from H, C_{1-4}alkyl, C_{1-4}alkylene-Z, $-CO-C_{1-4}$alkylene-Z, $-CO-C_{1-6}$alkyl, -COZ, Z and Z is selected from $-O-C_{1-4}$alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms selected from O, N and S and any aryl ring in R^{16} is optionally substituted by R^a and/or R^b as hereinabove defined;

where, T represents **$-(CH_2)_m-$** **[$-(CH_2)m-$]** where m is 1-4 and T is optionally monosubstituted with any value of R^{16} other than H; and

where T^1 represents **$-(CH_2)_{m^1}-$** **[$-(CH_2)m^1-$]** wherein m^1 is 0-4 and T^1 is optionally monosubstituted with any value of R^{16} other than H);

A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms where the heteroatoms are independently selected from O, N & S;

or a -S-S- dimer thereof when R^2=H; or a N-oxide thereof;

or a pharmaceutically acceptable salt, prodrug or solvate thereof.

The specification at the first paragraph on page 4, line 10 to page 6, line 11, has been further amended as follows:

(Twice Amended) In another aspect of the invention there is provided an inhibitor of ras farnesylation of Formula I

wherein:

R^1 is selected from H; $-C_{1-4}$alkyl; $-C_{1-3}$alkylene-Ph optionally mono or di-substituted on Ph with substituents selected from C_{1-4}alkyl, halogen, OH, C_{1-4}alkoxy, C_{1-4}alkanoyl,

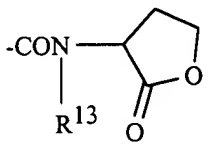
C_{1-4}alkanoyloxy, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, C_{1-4}alkanoylamino, nitro, cyano, carboxy, carbamoyl, C_{1-4}alkoxycarbonyl, thiol, C_{1-4}alkylsulfanyl, C_{1-4}alkylsulfinyl, C_{1-4}alkylsulfonyl and sulfonamido; -CO-C_{1-4}alkyl; -CO-O-C_{1-4}alkyl; -CO-O-C_{2-4}alkenyl; -CO-O-$(CH_2)_n$Ph optionally substituted on Ph as defined for substitution on Ph in R^1 = -C_{1-3}alkylene-Ph above and n=0-4;

-C_{1-4}alkylene-CONR^{4}R^5 where R^4 & R^5 are independently selected from H and C_{1-4}alkyl; and -C_{1-4}alkylene-COOR^6 where R^6 is selected from H, C_{1-4}alkyl;

R^2 is selected from H; -C_{1-4}alkyl; -C_{1-3}alkylene-Ph optionally substituted on Ph as defined for substitution on Ph in R^1 = -C_{1-3}alkylene-Ph above; -COC_{1-4}alkyl; and -COOC_{1-4}alkyl;

R^3 is selected from H; OH; CN; CF_3; NO_2; -C_{1-4} alkyl; -C_{1-4}alkylene-R^7 where R^7 is selected from phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms selected from O, N and S and any aryl ring in R^7 is optionally substituted as defined for substitution on the Ph group in R^1 = -C_{1-3}alkylene-Ph above; R^7; C_{2-4}alkenyl; halogen; -$(CH_2)_y$COOR^8 where y= 0-3 and R^8 represents H, C_{1-4}alkyl, or C_{2-4}alkenyl; -CONR^{9}R^{10} where R^9 and R^{10} independently represent H, C_{1-4}alkyl, C_{2-4}alkenyl, -O-C_{1-4}alkyl, -O-C_{2-4}alkenyl, -C_{1-3}alkylenePh optionally substituted as defined for this group for R^1 above; -CON(R^{11})OR^{12} where R^{11} and R^{12} independently represent H, C_{1-4}alkyl and C_{2-4}alkenyl;

a group of Formula II, -CONR^{13}-CHR^{14}-COOR^{17} , where R^{13} is H or C_{1-4}alkyl, R^{17} is H or C_{1-6}alkyl, R^{14} is selected from the side chain of a lipophilic amino acid, carbamoylC_{1-4}alkyl, N-(monoC_{1-4}alkyl)carbamoylC_{1-4}alkyl and **N-(diC_{1-4}alkyl)carbamoylC_{1-4}alkyl [N-(diC1-4alkyl)carbamoylC_{1-4}alkyl]**, the group of Formula II having L or D configuration at the chiral alpha carbon in the corresponding free amino acid; a lactone of formula



;

C_{1-4}alkyl monosubstituted on carbon with =N-OH;

a group of Formula -X-R^{15} where X is selected from O, CO, CH_2, S, SO, SO_2 and R^{15} is selected from C_{1-6}alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms selected from O, N and S and any aryl ring in R^{15} is optionally substituted as defined for the Ph group in R^1 = -C_{1-3}alkylene-Ph;

p is 0-3 in which R^3 values can be the same or different;

G is a linking moiety selected from the following groups written from left to right in Formula I:

-CO-NR^{16}- where R^{16} is selected from H, C_{1-4}alkyl, C_{1-4}alkylene-Z, -CO-C_{1-4}alkylene-Z, -CO-C_{1-6}alkyl, -COZ, Z and Z is selected from -O-C_{1-4}alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms selected from O, N and S and any aryl ring in R^{16} is optionally substituted as defined for the Ph group in R^1 = -C_{1-3}alkylene-Ph; -CH_2-NR^{18}- where R^{18} represents any value defined for R^{16}; -CH_2S-; -CH_2O-; -CH_2-CHR^{19}- where R^{19} represents any value defined for R^{16}; -CH=CR^{20}- where R^{20} represents any value defined for R^{16}; -CH_2NR^{21}-T- where R^{21} represents any value defined for R^{16}, T represents -$(CH_2)_w$- where w is 1-4 and T is optionally monosubstituted with R^{22} where R^{22} represents any value for R^{16} other than H; -CH_2NR^{23}-SO_2- where R^{23} represents any value defined for R^{16}; -CH_2-NR^{24}-CO-T- where R^{24} represents any value defined for R^{16}, T represents **-$(CH_2)_w$- [-$(CH^2)_w$-]** where **w [n]** is 0-4 and T is optionally monosubstituted with R^{29} where R^{29} represents any value for R^{16} other than H; -CO-NR^{25}-T- where R^{25} represents any value defined for R^{16}, T represents -$(CH_2)_w$- where w is 1-4 and T is optionally monosubstituted with R^{26} where R^{26} represents any value for R^{16} other than H; -CH_2S-T- where T represents -$(CH_2)_w$- where w is 1-4 and T is optionally monosubstituted with R^{27} where R^{27} represents any value for R^{16} other than H; -CH_2O-T- where T represents -$(CH_2)_w$- where w is 1-4 and T is optionally monosubstituted with R^{28} where R^{28} represents any value for R^{16} other than H;

A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms where the heteroatoms are independently selected from O, N & S;

or a -S-S- dimer thereof when R^2=H; or a N-oxide thereof;

or an enantiomer, diastereoisomer, pharmaceutically acceptable salt, prodrug or solvate thereof.

The specification at the first paragraph on page 10, line 4 to page 10, line 15, has been further amended as follows:

(Twice Amended) Suitable values for G= **$\underline{CH_2NR^{16}\ T}$ [$CHNR^{16}$ T]** include $CH_2.N(CO.CH_2.CHMe_2).CH_2.CH_2$; $CH_2.N(CH_2\ CH_2\ CH_2OMe).CH_2.CH_2$; $CH_2.N(CH_2.p\text{Ph.OMe}).CH_2.CH_2$; $CH_2.N(CO.CH_2.CHMe_2).CH_2$; $CH_2N(CO.CH_2.CH_2.CH_2.Me).CH_2$; $CH_2N(CO.CH_2.CHMe.CH_2Me).CH_2$; $CH_2N(CO.CH_2.CH_2.OMe)CH_2$; $CH_2N(CO.CH_2.\text{pyridin-3-yl}).CH_2$; $CH_2N(4\text{-methoxybenzyl})CH_2$; $CH_2N(CO.CH_2.CHMe_2)CH_2.CH_2.CH(Ph)$; $CH_2N(CO.CH_3)CH_2.CH_2.CH(Ph)$; $CH_2N(CO.CH_2.CHMe_2)CH_2$; $CH_2N(CO.CH_3)CH_2$; $CH_2N(CO.CH_2.CHMe_2)CH_2.CH(Ph)$; $CH_2N(CO.CH_2.CMe_3)CH_2.CH(Ph)$; $CH_2N(CO.CH_2.\text{pyridin-3-yl})CH_2.CH(Ph)$; $CH_2N(CO.1\text{-hydroxy-6-methoxy-pyridin-3-yl})CH_2.CH(Ph)$; $CH_2N(CO.CH_2\ \text{pyrid-3-yl})CH_2CH(Ph)$; $CH_2N(CO.CH_2CHMe_2)CH_2.CH_2$; $CH_2N(CO.CH_2CMe_3)CH_2.CH_2$; $CH_2N(CO\ \text{thiazol-2-yl})CH_2CH_2$; CH_2N $(CO\ 1\text{-oxido-6-hydroxypyridin-3-yl})CH_2CH_2$; $CH_2N(CO.CH_2\text{pyridin-3-yl})CH_2.CH_2$ and $CH_2N(CO.4\text{-methoxybenzyl})CH_2.CH_2$.

The specification at the third paragraph on page 10, line 20 to page 10, line 22, has been further amended as follows:

(Twice Amended) Suitable values for G = $-CH_2NR^{16}-$ include CH_2NH; CH_2NMe; $CH_2N(CO.CH_2.CHMe_2)$ and $CH_2N(CO.CH_2.CH_2.OMe)$. A preferred value for $-CH_2NR^{16}-$ is **$\underline{-CH_2NH-}$ [$-CH_2NH_2-$]**.

The specification at the fourth paragraph on page 10, line 23 to page 10, line 26 has been further amended as follows:

(Twice Amended) When G is **$\underline{-CH_2NR^{16}-T-}$ [$-CH_2NR16-T-$]** a suitable value for m is 1. When G is $-CH_2-NR^{16}-CO-T^1-$ a suitable value for m^1 is 1. When G is $-CH_2-NR^{16}-T-$ a

suitable value for m is 1. When G is $-CH_2-S-T-$ a suitable value for m is 1. When G is $-CH_2-O-T-$ a suitable value for m is 1.
G is especially -CONH-, $-CH_2.NH-$, $-CH_2NHSO_2-$., $-CH_2NHCO-$.

The specification at the first paragraph on page 32, line 4 to page 32, line 23, has been amended as follows:

(Twice Amended) Compounds of Formula I in which G represents $-CO-NR^{16}-$ may be prepared by forming an amide bond between compounds 1 and 2 as outlined in Scheme 1. Compounds of Formula I in which G represents $-CO-NR^{16}-T-$ may be prepared by an analogous procedure. Suitable coupling conditions include the following.

i) Use of EEDQ at ambient temperature in an organic solvent (e.g. **dichloromethane [dischloromethane]**, methanol).

ii) Use of oxalyl chloride in an organic solvent (e.g. CH_2Cl_2), DMF in a catalytic amount, in the presence of an organic base (e.g. NMM, triethylamine, DMAP) at 0°C to ambient temperature for 0.5-16h.

iii) Use of EDC/ HOBT in an organic solvent (e.g. DMF, CH_2Cl_2).

iv) Use of **DCCI/ HOBT [DCI/ HOBT]** in an organic solvent (e.g. DMF, CH_2Cl_2) in the presence of an organic base (e.g. triethylamine).

v) Use of mixed anhydride reactions under standard conditions, for example isopropylchloroformate in an organic solvent (e.g. DMF, DMA, dichloromethane) in the presence of an organic base (e.g. NMM, DMAP, triethylamine).

vi) Via an active ester under standard conditions e.g. pentafluorophenyl ester in an organic solvent (e.g. dichloromethane) in the presence of an organic base (e.g. triethylamine).

vii) Via an acid chloride under standard conditions e.g. using thionyl chloride and heat for about 150min followed by an organic base (e.g. triethylamine) in the presence of an organic solvent (e.g. acetonitrile).

The specification at the second paragraph on page 32, line 24 to page 33, line 3, has been further amended as follows:

(Twice Amended) Compounds of Formula I in which G represents $-CH_2NR^{16}-$, $-CH_2O-$ or $-CH_2S-$ may be prepared as outlined in Scheme 2. LG represents a leaving group (e.g. mesyloxy, tosyloxy, halogen) and X represents S, O or NR^{16}. Suitable coupling conditions include the following.

i) Use of an inorganic base (e.g. $NaHCO_3$, NaH, K_2CO_3, butyllithium) in an organic solvent (e.g. THF, DMF, DMSO) and a temperature of about 65° to 150°C

ii) **Use [Ue]** of an organic base (e.g. triethylamine, DMAP) in an organic solvent (e.g. THF, dichloromethane, DMA, DMF) at a temperature range of room temperature -150° C

iii) Use of an inorganic base (e.g. KOH, NaOH, K_2CO_3) in an aqueous (e.g. water) and organic solvents (e.g. dichloromethane) in a 2 phase system, optionally in the presence of a phase transfer catalyst (e.g. tetrabutylammoniumbromide).

The specification at the second paragraph on page 33, line 13 to page 33, line 18, has been amended as follows:

(Twice Amended) Compounds of Formula I in which G represents **$-CH_2-NR^{16}-$ [$-CH_2.NR^{16}-$]** may be prepared as outlined in Scheme 4 by coupling aldehyde (2) with compound 4. Suitable coupling conditions include the following.

i) Use of a reducing agent (e.g. $NaCNBH_3$, BH_3, hydrogen plus catalyst, $LiHBEt_3$, di-isobutyl-aluminiumhydride, lithium aluminium hydride, sodium borohydride) in the presence of a suitable solvent e.g. ethanol and acetic acid.

The specification at the fifth paragraph on page 33, line 28 to page 34, line 2, has been further amended as follows:

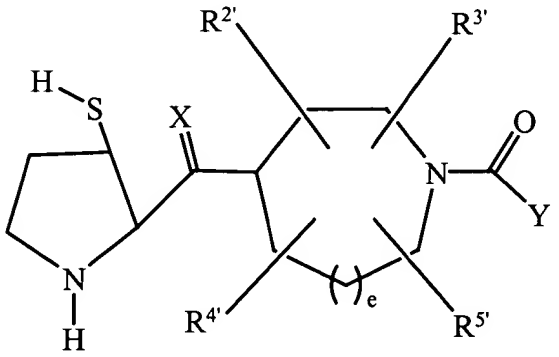
(Twice Amended) Compounds of Formula I in which G represents **$-CH_2-NR^{16}-T-$, $-CH_2-O-T-$ or $-CH_2-S-T-$ [$-CH_2.NR^{16}-T-$, $-CH_2.O-T-$ or $-CH_2.S-T-$]** may be prepared as outlined in Scheme 5 in which LG represents a leaving group (e.g. mesyloxy, tosyloxy, halogen) and X represents O, S or NR^{16}. Suitable coupling conditions are as outlined above

in relation to Scheme 2. Optionally the positions of LG and XH in compounds 1 and 2 in Scheme 5 can be reversed to give the same end product.

IN THE CLAIMS:

Claims 7 and 8 have been further amended as follows:

7. **(Three Times Amended)** A compound of the formula A:



B

wherein:

X is O or H_2;

e is 0;

t is 1 to 4;

$R^{2'}$, $R^{3'}$, $R^{4'}$, and $R^{5'}$ are independently selected from: H; C_{1-8}alkyl, alkenyl, alkynyl, aryl, heterocycle, -CO-$NR^{6'}R^{7'}$ or -CO-$OR^{6'}$, unsubstituted or substituted with one or more of:

1) aryl or heterocycle, unsubstituted or substituted with:
   a. C_{1-4}alkyl,
   b. **$(CH_2)_tOR^{6'}$ [$(CH_2)tOR^{6'}$]**,
   c. **$(CH_2)_tNR^{6'}R^{7'}$ [$(CH_2)tNR^{6'}R^{7'}$]**,
   d. halogen,
2) C_{3-6}cycloalkyl,
3) $OR^{6'}$,

4) $SR^{6'}$, $S(O)R^{6'}$, $SO_2R^{6'}$,

5) $-NR^{6'}R^{7'}$,

6) $-NR^{6'}-CO-R^{7'}$,

7) $-NR^{6'}-CO-NR^{7'}R^{8'}$,

8) $-O-CO-NR^{6'}R^{7'}$,

9) $-O-CO-OR^{6'}$,

10) $-O-NR^{6'}R^{7'}$,

11) $-SO_2NR^{6'}R^{7'}$,

12) $-NR^{6'}-SO_2-R^{7'}$,

13) $-CO-R^{6'}$, or

14) $-CO-OR^{6'}$;

and any two of $R^{2'}$, $R^{3'}$, $R^{4'}$, and $R^{5'}$ are optionally attached to the same carbon atom;

Y is aryl, heterocycle, unsubstituted or substituted with one or more of:

1) C_{1-4}alkyl, unsubstituted or substituted with:

   a. C_{1-4}alkoxy,

   b. $NR^{6'}R^{7'}$,

   c. C_{3-6}cycloalkyl,

   d. aryl or heterocycle,

   e. HO,

2) aryl or heterocycle,

3) halogen,

4) $OR^{6'}$,

5) $NR^{6'}R^{7'}$,

6) CN

7) NO_2, or

8) CF_3;

$R^{6'}$, $R^{7'}$ and $R^{8'}$ are independently selected from: H; C_{1-4}alkyl, C_{3-6}cycloalkyl, heterocycle, aryl, aroyl, heteroaroyl, arylsulfonyl, heteroarylsulfonyl, unsubstituted or substituted with:

a) C_{1-4}alkoxy,

b) aryl or heterocycle,

c) halogen,

d) HO,

e) $-CO-R^{9'}$,

f) $-SO_2R^{9'}$, wherein

$R^{6'}$ and $R^{7'}$ may be joined in a ring, and

$R^{7'}$ and $R^{8'}$ may be joined in a ring;

$R^{9'}$ is C_{1-4}alkyl or aralkyl;

a pharmaceutically acceptable salt thereof.

8. **(Three Times Amended)** The compound **(2S)-2-(2-methoxy-ethyl)-1-((cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-4-naphthoyl-piperazine [(2S)-2-(2-methoxyethyl)-1-((cis)-3-sulfanyl-pyrrolidin-2-ylmethyl)-4-naphthoyl-piperazine]** or a pharmaceutically acceptable salt thereof.